REMARKS

Claims 43 to 59 are pending. Applicants respectfully request entry of the remarks made herein into the file history of the present application.

I. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 56 and 57 are rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. In particular, the Examiner alleges that claims 56 and 57, which recite "wherein the patient displays one or more atypical moles" does not further limit the scope of independent claims 43 and 45, because a patient in need of treatment for melanoma would have at least one atypical mole. Applicants respectfully disagree for the reasons set forth below.

According to the applicable case law, the definiteness requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamide Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986).

The specification as originally filed describes melanomas to be malignant neoplasms which are aggressive, frequently metastatic tumors derived from either melanocytes (pigment producing cells of the epidermis that are restricted to the basal layer of the epidermis) or melanocyte related nevus cells (pigmented spots on the skin, such as moles) (*see, e.g.,* the specification at p. 3, line 3 to p. 5, line 24). The specification as originally filed defines the term "atypical mole" to mean a mole with features that are abnormal and may be precancerous (*see, e.g.,* the specification at p. 18, lines 5 to 6). One skilled in the art would understand from the specification that the presence of an atypical mole is a predictor of melanoma such that some patients develop tumors that are derived from atypical moles. However, the skilled artisan would also understand from the specification that a patient can have a melanoma tumor that is derived from melanocytes alone and that such patient would not necessarily display an atypical mole. The specification does not teach or suggest that a patient in need of treatment for melanoma would necessarily have at least one atypical mole. Thus, Applicants respectfully submit that one skilled in the art would understand that claims

56 and 57 do indeed limit independent claims 43 and 45 because not all patients that are in need of treatment for melanoma will necessarily display at least one atypical mole.

As such, Applicants submit that claims 56 and 57 are definite and that the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

II. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected claim 43 under 35 U.S.C. § 112, first paragraph for lack of enablement. In particular, the Examiner alleges that while the specification is enabling for the selective antagonism of the ETB receptor in a patient having melanoma comprising the administration of known peptide and antibody antagonists, the instant specification does not reasonably provide enablement for the administration of an ETB antisense molecule or ribozyme targeting the ETB receptor. In particular, the Examiner contends that a skilled artisan would require undue experimentation to make and use the invention as of the filing date of the present application because the attainment of any therapeutic effect in any patient via gene therapy was unpredictable and the specification fails to provide any guidance for a skilled artisan on how to overcome the hurdle of *in vivo* vector targeting to desired tissues/organs so that an efficient gene delivery can be attained in the tissue/organ.

Applicants submit that the Examiner has not made an enablement rejection over the *claimed* method. "The invention that one skilled in the art must be enabled to make and use is *that defined by the claims* of the particular application or patent". See *M.P.E.P.* § 2164 (emphasis added). Claim 43 is directed to a method for treating melanoma in a patient in need thereof, comprising selectively antagonizing the endothelin B receptor (ETB) in said patient.

Applicants submit that if multiple uses for the claimed invention are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. See M.P.E.P § 2164.01(c). Applicants submit, and the Examiner has also acknowledged, that the specification is enabling for the selective antagonism of the ETB receptor in a patient having melanoma comprising the administration of known peptide and antibody antagonists. Thus, Applicants have provided at least one enabled use, although multiple uses are disclosed in the specification. Hence, the application is enabling for the claimed invention.

Moreover, although the specification teaches multiple treatment methods that fall within the scope of the claim, one skilled in the art can readily determine which treatment methods would be more effective than others and can identify many methods that the claim encompasses. Since the law does not require a disclosure of a test with every species encompassed by a claim even in an unpredictable art, the present invention is enabled. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 216 (CCPA 1971). Mere unpredictablity of the result of an experiment is not a consideration. *Id.*, at 504, 219. Since the present application has provided detailed guidance in the specification for one skilled in the art to perform routine experimentation to test various methods encompassed by the claims, the invention is enabled.

For the foregoing reasons, Applicants respectfully request that the claim rejections under Section §112, first paragraph, be withdrawn.

III. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

1. The Pending Claims Are Not Obvious Over Kikuchi in view of Vournakis

Claims 33, 37 and 39-42 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi *et al.*, 1996, Biochem. Biophys. Res. Comm. 219:734-739 ("Kikuchi") in view of U.S. Patent No. 6,063,911 to Vournakis *et al.* ("Vournakis").

Applicants do not agree that the proposed combination of art renders obvious the claimed invention; however, to advance prosecution and to reduce the outstanding issues, Applicants filed on July 24, 2006 a Declaration of Dr. Robert J. Schneider and Dr. Sumayah Jamal under 37 C.F.R. § 1.13 ("the Declaration") which establishes that the claimed invention was made prior to the effective date of Vournakis, a copy of which is submitted herewith. Applicants further submit herewith a Supplemental Declaration of Dr. Robert J. Schneider and Dr. Sumayah Jamal under 37 C.F.R. § 1.131 ("the Supplemental Declaration"), which confirms that all activities stated in the Declaration, including the conception and reduction to practice of the present invention, occurred in the United States (see the Supplemental Declaration at para. 4). Accordingly, Vournakis is not available as prior art and the rejection under 35 U.S.C. 103(a) should be withdrawn.

2. The Pending Claims Are Not Obvious over Kikuchi

Claims 43-46, 48, 50, 53, and 56-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. *M.P.E.P.* 2143. Applicants submit that Kikuchi fails to satisfy any requirements for establishing obviousness for the reasons discussed below and respectfully request that the rejection of claims 43-46, 48, 50, 53, and 56-59 be withdrawn on that basis.

The present invention is directed to methods of treating melanoma comprising selectively antagonizing the ETB receptor or administering a therapeutically effective amount of selective endothelin B receptor antagonist to a patient in need thereof.

The Examiner alleges that Kikuchi provides the motivation for a person having ordinary skill in the art at the time the invention was made to administer BQ-788 to a patient having primary melanoma or a recurrent melanoma expressing the ETB receptor. Applicants disagree respectfully. Kikuchi teaches that primary cutaneous melanoma cells express ETB, and that such cells show increased DNA synthesis in response to ET-1 treatment *in vitro*. Kikuchi also teaches that an ETB-selective receptor antagonist, BQ-788, attenuates DNA synthesis of primary cutaneous melanoma cells that were treated with ET-1. In contrast to the primary melanoma cell lines tested, Kikuchi further teaches that the growth of metastatic melanoma cells in response to ET was decreased. Metastatic cell lines show downregulation of ETB, and do not respond to ET-1 treatment. Hence, contrary to the Examiner's allegation, the teachings of Kikuchi actually suggest that BQ-788 **should not** be administered for the treatment of melanoma. Since Kikuchi teaches that the effects of BQ-788 on the inhibition of DNA synthesis in metastatic melanoma cells is significantly reduced, this would suggest to one skilled in the art that the drug is not specifically well qualified in the treatment of melanomas.

Furthermore, the mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills,* 16 USPQ2d 1430 (Fed. Cir. 1990); *M.P.E.P.* § 2143.01. The skilled artisan would have hardly thought it desirable to treat melanoma with a selective inhibitor of ETB receptor because Kikuchi suggests that

attempting treatment of melanoma with such an inhibitor would be ineffective due to the decreased growth of metastatic melanoma cells in response to ET. Even after reading the title of Kikuchi, "Decreased ETB Receptor Expression in Human Metastatic Melanoma Cells", the skilled artisan would think it undesirable to treat melanoma with a selective antagonist of an ETB receptor since ETB expression is decreased in metastatic melanoma cells than in primary melanoma cells. Applicants submit that Kikuchi teaches away from the claimed invention and it would have been undesirable and counterintuitive for the skilled artisan to administer BQ-788 for the treatment of melanoma based on the teachings of Kikuchi.

Kikuchi's remarks that the ETB receptor might be necessary in tumor evolution cannot be interpreted as a clear incentive to use BQ-788 to treat cancer by acting on the early stages of melanoma (see Kikuchi at page 739, last sentence). In fact, as Kikuchi teaches that ETB is downregulated in metastatic melanoma, a skilled artisan would not conclude that ETB is involved in melanoma progression. Instead, Kikuchi's teachings would likely have the opposite effect. One skilled in the art would conclude from the teachings in Kikuchi that the **downregulation** of the ETB receptor may be involved in the progression of primary melanoma to metastatic melanoma. Accordingly, Kikuchi generated considerable uncertainty as to whether the inhibition of ETB via administration of BQ-788 would be effective in reversing the progression of primary melanoma to metastatic melanoma. Thus, Kikuchi does not provide one of ordinary skill in the art with a reasonable expectation of success in achieving the claimed invention.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *M.P.E.P.* 2143.03. Kikuchi neither teaches nor suggests methods of treating melanoma comprising administering a therapeutically effective amount of a selective endothelin B receptor antagonist to a patient in need thereof. Kikuchi's investigations are not concerned with the treatment of melanoma, but rather with comparing the expression of ET receptors between human primary and metastatic melanoma and studying the mitogenic effects of ET on various melanoma cell lines (see Kikuchi at page 734). Kikuchi does not teach or suggest each and every limitation of the claimed invention, and thus, the rejection cannot stand.

In view of the foregoing, Applicants submit that the teachings of Kikuchi do not make obvious the methods of the claimed invention for the treatment of melanoma. Therefore, Applicants respectfully request that the rejection of claims 43-46, 48, 50, 53, and 56-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi be withdrawn.

3. The Pending Claims Are Not Obvious over Kikuchi in view of Battistini

Claims 43-46, 48, 50-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi in view of Battistini *et al.*, 1998, Pulmonary Pharmacology and Therapeutics. 11:97-112 ("Battistini").

Battistini discusses the use of several selective ET receptor antagonists, such as IRL-1038, RES-701-1 and BQ-788, in order to inhibit the effects induced by ETs. The Examiner alleges that it would have been prima facie obvious at the time the claimed invention was made to substitute IRL-1038 or RES-701 for the BQ-788 taught by Kikuchi.

As discussed above, the teachings of Kikuchi do not make obvious the methods of the invention for the treatment of melanoma. Since the teachings of Kikuchi do not suggest the desirability of administering BQ-788 to selectively antagonize the ETB receptor for the treatment of melanoma in patients, there would certainly be no motivation for one skilled in the art to substitute IRL-1038 or RES-701 for the BQ-788 taught by Kikuchi.

Furthermore, Battistini does not cure the deficiencies of Kikuchi. Battistini neither teaches nor suggests methods of treating melanoma comprising administering a therapeutically effective amount of a selective endothelin B receptor antagonist, including ETB IRL-1038, RES-701-1 or BQ-788, to a patient in need thereof. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *M.P.E.P.* 2143.03. Neither Kikuchi nor Battistini by themselves or combined disclose each and every limitation of the claimed invention, and thus, the rejection cannot stand.

Applicants respectfully request that the rejection of claims 43-46, 48, 50-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi in view of Battistini be withdrawn.

4. The Pending Claims Are Not Obvious over Kilkuchi in view of Ferrara

Claims 43-50, 53, and 56-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi in view of in view of U.S. Patent No. 5,573,762 to Ferrara *et al.* ("Ferrara").

Ferrara teaches the use of endothelin antagonists, including antibodies and inhibitory peptides, for the treatment of cardiac hypertrophy. The Examiner alleged that it would have been prima facie obvious at the time the invention was made to substitute an anti-endothelin B antagonistic antibody, as taught in Ferrara, for the BQ-788 taught by Kikuchi.

As discussed above, the teachings of Kikuchi do not make obvious the methods of the invention for the treatment of melanoma. Since the teachings of Kikuchi do not suggest the desirability of administering BQ-788 to selectively antagonize the ETB receptor for the treatment of melanoma in patients, there would certainly be no motivation for one skilled in the art to substitute an anti-endothelin B antagonistic antibody for the BQ-788 taught by Kikuchi.

Furthermore, Ferrara does not cure the deficiencies of Kikuchi. Ferrara neither teaches nor suggests methods of treating melanoma comprising administering a therapeutically effective amount of a selective endothelin B receptor antagonist, including an anti-endothelin B antagonistic antibody, to a patient in need thereof. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *M.P.E.P.* 2143.03. Neither Kikuchi nor Ferrara by themselves or combined disclose each and every limitation of the claimed invention, and thus, the rejection cannot stand.

Applicants respectfully request that the rejection of claims 43-50, 53, and 56-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi in view of Ferrara be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the rejections in the previous Office Action and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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